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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
CLARK, D	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/993,564	Applicant(s) NEWMAN, STUART A.	
	Examiner Deborah J. R. Clark	Art Unit 1633	

-- The MAILING DATE of this communication app ars on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☒ Responsive to communication(s) filed on *01 May 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☐ Claim(s) *1-7,13,16,28-34,38-48,50,53 and 55-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-7,13,16,28-34,38-48,50,53 and 55-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)

16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 16 .

18)☐ Interview Summary (PTO-413) Paper No(s). _____ .

19)☐ Notice of Informal Patent Application (PTO-152)

20)☐ Other: .

DETAILED ACTION

Continued Prosecution Application

1. The request filed on 05/01/00 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/993,564 is acceptable and a CPA has been established. An action on the CPA follows.

2. Applicant's "preliminary amendment and response" to the previous office action, filed 05/01/00, has been received. Claims 1-7, 10, 13, 16, 28-34, 38-48, 50, 53, and 55-71 are now pending.

Claim Rejections - 35 USC § 101

3. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

4. Claims 1-7, 13, 16, 28-34, and 39-48 stand, and newly presented claims 56-71 are, rejected under 35 USC 101 as directed to nonstatutory subject matter for reasons of record.

Applicant argues that the invention is not a human being and that no statutory authority supports the rejection on these grounds. This argument is not deemed persuasive for reasons discussed fully below.

Applicant argues that he does not support the patentability of subject matter "embracing human beings", and states that the original examiner coined the phrase in the first office action (see paper no. 15, page no. 7). No matter who coined the phrase, the pending claims encompass or "embrace" human beings. By applicant's argument he is supporting the patentability of such

claims. Applicant's state that the invention does not "embrace a human being". The examiner does not agree. The claims are directed to chimeric animals or embryos which are made up of cells of at least two species one of which is human. There is no limitation in the claims that specify what percentage of the embryo or animal is human and what percentage is made up of cells of the second or other species. See, for example, paper no. 15, page 36 ("[t]he claimed invention is not limited to a specific degree or range of chimerism or chimeric lifetime. All such variations are within the subject matter of the invention."). Because the embryo or animal could consist of primarily human cells and only a small insignificant amount of cells being from the other organism, the embryo or animal could be considered human. An analogous example would be a human who has received a porcine heart transplant. This human remains a human. A human is not considered to be no longer human because it has cells from another animal species within the body. Therefore, applicant's argument is not persuasive.

Applicant states that the PTO does not have the authority to reject an application as "embracing a human being" (see paper no. 15, page 7). Under 35 U.S.C. 131 it is the responsibility of the PTO to determine whether the applicant is entitled to a patent under the law. In doing this the PTO considers the statutes, case decisions, and interpretations thereof.

Applicant argues that chimeras containing human cells have been reported, and these are clearly not considered to be human (see paper no. 15, page 8). However, none of the rejected claims are limited as such. The chimeras referred to in the cited prior art were made from an animal, embryo, or fetus of one species into which was added only one specific type of human cells. Therefore, the animal was not considered to be human. The claimed invention is much different in that embryonic cells of the two or more species are mixed and then an embryo is

allowed to develop. Therefore, in that case it is not clear as to what portion of the chimera is human or otherwise. There is no limitation upon which type of cells would be human and which would be of the other species. In the prior art the contribution of the human cells were limited by the type of cells implanted. Only at least partially differentiated human cells were transplanted. In the instant claims, the human cells would purportedly have the ability to differentiate into any or all cells. For instance, an example would be where the animal was made up of human cells, but for one particular type or locale of cells. Therefore, such an animal could be considered human. An organism resulting from such a fact pattern is encompassed by the instantly claimed invention.

Applicant alleges that nowhere does the statute restrict patentability based upon embracing a human being and that *Diamond v. Chakrabarty,* 447 US 303 (1980) does not provide a basis for the present rejection. The examiner does not agree. When Congress does not specifically address a question of statutory interpretation, the statutory provision should be interpreted with a view to its place in the overall statutory scheme, not in isolation. *FDA v. Brown & Williamson Tobacco Corp.*, 120 S.Ct. 1291, 2000 U.S. LEXIS 2195, 146 L.Ed.2d 121, slip op. at 9 (2000). Congress has not specifically addressed the question of whether the terms "machine, manufacture, or composition of matter," as they are used in the patent statutes, include a human being. Similarly, the Court in Chakrabarty did not address whether human beings are patentable subject matter.

Applicant argues that the Federal Circuit recently emphasized in *State Street Bank & Trust Co. v. Signature Financial Group,* 149 F.3d 1368 (Fed. Cir. 1998) that neither the courts nor the Patent Office are authorized to embellish the statutory requirements for patentability (see

paper no. 15, page 11). However, it is noted that the court also stated in the same paragraph that "Thus, it is improper to read limitations into §101 on the subject matter that may be patented where the legislative history indicates that Congress clearly did not intend such limitations." In this instance, it is not clear that Congress ever directly addressed this issue, nor can it be inferred from the absence of any express intent that Congress enacted section 101 to cover human beings as eligible for patenting.

Applicant states that the Federal Circuit has held clearly in *State Street* that any invention made by man is patentable subject matter (see paper no. 15, page 12). However, the Federal Circuit has not considered the patentability of human beings. Applicant argues that it is for Congress, not the courts or the USPTO, to set forth any limitations on patentable subject matter. However, the USPTO is charged with the determination of patentability on a case-by-case basis. To make this determination the USPTO relies upon the statutes and the interpretations thereof by the USPTO's reviewing courts and administers the law accordingly. When there are paramount patent issues of first impression, in the absence of clear legislative intent and guidance from the courts, it is incumbent on the Office to proceed cautiously.

Applicant alleges that the examiner has not specified how the claimed man-made chimeras "embrace a human being" or what features of a human are critical in doing so and that the claims can be considered to embrace a human being only in extreme cases and only in a subjective sense (see page 12, last full ¶). The examiner has explained why human beings fall within the scope of the claims and has given examples as to why this is so (see above and in previous office actions). Further, even if a human being is encompassed only in extreme cases a human being is nevertheless encompassed. Applicant argues that chimeras by definition are not

human, however, the examiner does not agree. Nowhere are chimeras defined as necessarily non-human. Applicant argues that embryos which are not exclusively human in origin do not fall under the limitations discussed above. The examiner does not agree. As stated above, an embryo with human cells, but for a small percentage or perhaps one cell type, is considered human.

Applicant argues that the Office has not held that prior art chimeras were human because they contained human cells (see paper no. 15, pages 13-14). However, the claims herein are not limited to such a scenario. The prior art as described by applicant contains only a limited type of human cells or only few human cells compared to the other species. Further, the assignment of prior art constructs to a statutory class of invention is not at issue. The pending claims are much broader than these scenarios and include situations of the reverse, wherein only a few cells or a particular cell type are of the non-human species.

Applicant alleges that the PTO is confusing the claimed invention with that of grafts or transplants between species. Applicant further argues that if the embryo develops with 99% human cells and 1% non-human primate cells, the resultant embryo is not human. The examiner does not agree. There is no prerequisite degree of contribution from either species of the chimera. The chimera could develop with all human cells, but for one specific type of cell. It is the examiner's position that in such instances the claimed embryo embraces humans.

Applicant has attached in exhibit A copies of patents that have issued that they claim would "embrace a human being". The information provided in Exhibit A is irrelevant, and the only patent therein which includes copies of the claims, has claims directed solely to a mouse. Each application is examined on its own merits on a case-by-case basis. *See In re Alappat,*

33 F.3d 1526, 1569 n.2, 31 USPQ2d 1545, 1579 n.2 (Fed. Cir. 1994) (Newman, J., concurring) (statutory subject matter jurisprudence has developed case by case).

In conclusion, claims 1-7, 13, 16, 28-34, and 39-48 stand, and newly presented claims 56-71 are, rejected under 35 USC 101 for reasons of record.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. The rejection set forth under 35 USC 102(b) over Zanjani et al. or Almeida-Porada et al. is overcome by applicant's amendment. Applicant has amended each of the rejected claims to recite that the animal or embryo is made up of human cells and non-human primate cells. Zanjani et al. and Almeida-Porada et al. do not disclose an animal or embryo comprising human and non-human primate cells.

7. Claims 28, 29, and 32-34 stand rejected under 35 USC 102(b) as anticipated by Pixley et al. for reasons of record.

Applicant does not argue the rejection over Pixley et al. separately, but together with the above recited rejection. However, the rejected claims include the scenario where the second animal species is mouse. Therefore, the disclosure of Pixley et al. continues to anticipate the pending claims.

Applicant argues that the chimeras of Pixley et al. do not fall within any generally accepted definition in the art of a chimera (see paper no. 15, page 16). The examiner does not agree. A chimera is defined as an organism made up of two or more tissues of different genetic composition (see prior office actions). Therefore, the organism disclosed by Pixley et al. falls squarely into the definition.

Applicant argues that true chimeras do not result from xenografts or transplants of adult or differentiated cells. The examiner does not agree. Xenografts, xenotransplants, or even allografts or allotransplants fall squarely into the definition of chimeras.

Applicant rejects the definition sited by the examiner in the previous office action and point out that in Dorland's Medical Dictionary a chimera is defined as "an individual organism whose body contains cell populations derived from different zygotes of the same or different species, occurring spontaneously, as in twins (blood group chimeras) or produced artificially, as an organism which develops from combined portions of different embryos, or one in which tissues or cells from another organism have been introduced." The examiner points out the final phrase "**or one in which tissues or cells from another organism have been introduced**" (emphasis added). Therefore, the disclosed organism of Pixley et al. falls within this definition.

Applicant argues that they are claiming chimeras in Dorland's first sense, however, the specification does not recite any particular definition which would limit the claims to garner such limitation (see *In re Morris*, 127 F.3d 1048, 1054, 44 USPQ2d 1023, 1027 (Fed. Cir. 1997)("[T]he PTO applies to the verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary

skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in the applicant's specification.")).

Applicant argues that they are describing embryos where aggregation of totipotent cells of two or more species is performed (see paper no. 15, page 18). However, none of the rejected claims are so limited.

Therefore, claims 28, 29, and 32-34 stand rejected as anticipated by Pixley et al.

8. The rejection set forth under 35 USC 102(b) over Cheng et al. is overcome by applicant's amendment. Applicant has amended each of the rejected claims to recite that the cell line is isolated from a chimeric animal or embryo made up of human cells and non-human primate cells. Cheng et al. do not disclose a human or non-human primate embryonic cell line.

9. Claim 10 stands, and newly presented claim 68 is, rejected under 35 USC 102(b) as anticipated by ATCC entries HTB 157, 158, and 160, page 271, for reasons of record.

Applicant argues again that cells derived from chimeras would differ in immunological properties (see paper no. 15, page 19). However, this would depend upon the cell type. Applicant argues that in an immunological assay one would only be concerned with the cells bearing immunological capacity. However, the claims are directed to a cell line of any cell type. Applicant argues that cells not involved in immune responses would be valuable in studying the development of the chimeric embryos, cell lines, and animals. However, applicant is reminded that the claims are directed to the product, the product being a cell line. The intended use is not applicable when determining the novelty of the product unless the prior art product would not be expected to be able to be used in a manner specified in a positive claim limitation. See MPEP 2112.01.

Applicant argues that embryo aggregation chimeras would be expected to be immunologically unprecedented as they would be tolerant to grafts from both species used. However, again applicant is reminded that the cells are directed to a cell line, not an embryo. Applicant states that lymphocytes and Langerhans dendritic cells would have different patterns of gene expression. However, the cell lines are not limited to these types of cells.

The point made regarding transgenes is withdrawn as claims 11 and 12 have been canceled.

In conclusion, claim 10 stands, and newly presented claim 68 is, rejected under 35 USC 102(b) for reasons of record.

10. Claims 10, 50, and 68 are rejected under 35 U.S.C. 102(b) as being anticipated by ATCC, entry CRL-2378, designated MA-104.

MA-104 was deposited with the ATCC in May, 1994. MA-104 is a cell line isolated from the embryonic kidney tissue of a Rhesus monkey. Therefore, the claims are anticipated because cells isolated and used to generate a cell line may not include both species, but only one of the species. The breadth of the claims would encompass a cell line isolated from embryonic kidney tissue of a Rhesus monkey.

11. The rejection set forth under 35 USC 102(b) over Bradley et al. is overcome by applicant's amendment. Applicant has amended each of the rejected claims to recite that the animal or embryo is made up of human cells and non-human primate. Bradley et al. do not disclose an animal or embryo comprising human and/or non-human primate cells.

12. Claims 13, 66, 67, and 69-71 are rejected under 35 U.S.C. 102(b) as being anticipated by Starzl et al.

. Starzl et al. discusses humans in which baboon kidneys or livers were transplanted and the resulting chimerism of the patient (see pages 214, 215, and 219). On page 219 Starzl et al. states that the graft and the recipient became genetic composites. It is noted that certain claims recite that the chimeric animal was made or not made in a particular way. However, process limitations are not given weight in consideration of the product claims unless they define the product itself. Because the breadth of the claims encompasses the humans disclosed by Starzl et al., there is no change to the product garnered by the method of making. Applicant is referred to MPEP 2113 for a discussion on Product-by-Process type claims.

13. Claim 16 is rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over humans or non-human primates as found in nature.

Claim 16 is directed to a descendant of the chimeric animal of claim 13. The descendant of the chimeric animal is not necessarily any different from one of the source species. There is no limitation that the descendant is chimeric. Individual germ cells would represent only one species. Therefore, if the germ cell which was subsequently used in reproduction was human, and a human was used as a mate, then the descendant would be totally human. If the germ cell which subsequently was used in reproduction was non-human primate and a same species non-human primate was used as a mate, then the descendant is a non-human primate of singular species. The descendant would not be any different from non-human primates or humans known in the art and found in nature. Therefore, the descendant would be anticipated by, or obvious over known humans and non-human primates.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 1, 2, 5, 28, 29, 32-34, and 38-48 stand, and newly presented claims 56, 57, and 59-65 are rejected under 35 USC 103 as obvious over Gustafson et al. for reasons of record.

Applicant argues that Gustafson et al. does not provide motivation or teaching to make chimeric embryos with human cells (see paper no. 15, page 24). The examiner does not agree. Because Gustafson et al. discloses sheep-goat chimeras, the art itself in combination with Gustafson would motivate one of skill in the art to make aggregates including human cells.

Applicant argues that the times that the paper was cited in the literature demonstrates that one of skill in the art would not have been motivated to use human cells. However, the fact that one chose not to do something does not mean that it would not have been obvious to have done so.

Applicant argues that the examiner did not point out the motivation offered by Gustafson and that persons who have relied upon Gustafson have not been so motivated. However, the teaching of Gustafson and the knowledge and desires in the prior art in combination provide such motivation. Motivation does not have to be found specifically in a prior art reference, but can be taken from the general state of the art itself (see MPEP 2143.01 and In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992)). As applicant acknowledges, other chimeras were known and there was a desire in the art to study development. Therefore, motivation existed at the time of invention to modify the

teaching of Gustafson to include human/non-human-primate aggregates. Applicant alleges that Gustafson was actually a teaching away because the references relying on Gustafson did so in the context of embryo mortality, not formation. However, this is irrelevant. If there was a teaching away it would need to be found directly in Gustafson not in a summarized relation of the disclosure which relies thereon. Further, the use of the embryo is irrelevant. Even if the embryo was made to determine mortality, it would still have been made. Therefore, the rejection is maintained for reasons of record.

16. The rejection made previously over Watanabe et al. in view of Robertson et al. is withdrawn based upon applicant's amendment.

Claim Rejections - 35 USC § 112

17. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

18. Claims 39-48 and 55 stand rejected under 35 USC 112, 1st paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record.

Applicant provides clarification as to the intended meaning of the embryo's viability (see paper no. 15, page 29). However, it remains that the specification does not disclose such embryos. Applicant states that there is no requirement that the period of viability will be known

in advance. However, if the claim specifically recites a limitation, said limitation must be disclosed in the specification.

In regards to the claims that recite "termination", applicant argues that the embryos would be useful to investigators. However, the usefulness is not at issue here. Rather, the disclosure of the invention is at question. 35 USC 112, 1st paragraph requires that the specification disclose the invention.

Applicant states that on page 5 it is stated that the embryos can be propagated for varying periods. However, where the claims recite a specific limitation, i.e. a specific time, this time must have been disclosed in the specification.

19. Claims 56 and 57 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 56 requires that the chimeric embryo exhibit composite morphology. Claim 57 requires that the chimeric embryo exhibits multi-tissue chimerism.

The specification does not disclose that the chimeric embryo would exhibit composite morphology or multi-tissue chimerism. These limitations constitute new matter. The specification does not disclose an embryo with composite morphology or multi-tissue chimerism nor does it describe how to make such an embryo or how to determine whether an embryo has these characteristics. The specification does not provide adequate written description of the claimed invention. The specification describes human/non-human animal chimeric animals or embryos which will develop into animals (see, e.g. pages 7-9 of the specification). The

specification does not recite multi-tissue chimerism or composite morphology. There is no explicit or implied support for embryos which have multi-tissue chimerism or composite morphology. Therefore, the instant specification does not provide written description of the claimed invention.

20. Claims 1-7, 10, 13, 16, 28-34, 38-48, 50, 53, and 55-71 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant specification does not provide an adequate written disclosure of the claimed invention. The claims are directed to chimeric embryos or animals and cell lines for these embryos or animals comprising human cells and non-human primate cells. The claims encompass embryos, animals, and cell lines with any degree of chimerism and with as yet undefined features. The functionalities of the system(s) of the organism is unknown because it is undefined as to the contribution of each species to each system.

The specification does not disclose the essential features of the claimed chimeras. The specification describes that chimeras as having any or an unspecified degree of chimerism. The specification does not disclose what contribution each species would make to the chimera.

The written description is insufficient to inform a skilled artisan that applicant was in possession of the claimed invention as a whole at the time the application was filed. The specification reads as prophetic and no specific description of the chimeras is set forth. The ultimate structure, physical and anatomical, is not set forth. The contribution that each species makes to the chimera is not set forth. One cannot envision the chimera because it is unknown as

to the functionality of the organ systems, or what organ systems would have attributes of what species.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

The skilled artisan cannot envision the detailed structure of the encompassed chimeras, cell lines, or animals, and therefore conception is not achieved. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of making it. A description of the final product is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence. The claims pending herein cover a chimera of human and any non-human primate. No description of such chimeras is provided because it is not clear what the final product's structure would be.

Therefore, the claims do not meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

21. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

22. Claims 1-7, 10, 13, 16, 28-34, 38-48, 50, 53, and 55 stand, and newly presented claims 56-71 are, rejected under 35 USC 112, 1st paragraph for failing to teach how to make and use the invention for reasons of record.

Applicant alleges that the technology for producing chimeric mammalian embryos is "robust", i.e., insensitive to variations in procedure, species origin of the cells, or species origin of the zona pellucida (see paper no. 15, page 31). The examiner does not agree. Very few species have been used in making chimeric embryos. Mouse-rat and sheep-goats are the only mammalian species that were known to have been used for making chimeric embryos at the time of applicant's invention. Applicant alleges that techniques developed for mouse embryo culture, sheep embryo culture, mouse-mouse, and mouse-rat chimeras have proved successful for sheep-goat chimera production. However, applicant is grossly overstating the state of the art. Further, the instant claims now require human and non-human primate chimeric embryos. None of the prior art methods enable one to culture primate embryos. As pointed out in the prior office action, primate embryos are quite different from other species. For instance, primate embryos form an egg cylinder instead of an egg disc and primate embryos must secrete chorionic gonadotropin whereas the other species do not. Therefore, it is unpredictable as to whether the

culture methods used in mouse, rat, sheep, or goats could be extrapolated to primate embryos. Applicant argues that the differences cited by the examiner reflect the utility of these techniques across species. This is not the case. The specification must enable both how to use and how to make the claimed invention. The instant specification enables neither. Though one of skill in the art could easily mix together embryonic cells of two species, the formation of a cooperative entity and it's viability for any length of time is completely unpredictable. Therefore, the specification does not enable how to make the claimed embryos, cell lines, or animals. Because the embryo is not expected to be viable and become an animal, and because the contribution of the species upon the final animal, if produced, is unpredictable, the specification does not enable how to use the claimed invention.

Applicant alleges that once an experimental protocol is established in one species the technology is transferable to other species (see paper no. 15, ¶ bridging pages 31-32). Applicant cites the prior art where cloning was used in different species. However, it should be recognized that even in this particular art, it took several years before pigs could be cloned. There was no direct transfer of the technology. It took much unpredictable trial and error experimentation before the pigs were cloned. Further, in regards to other biotechnology arts it can be shown that technology cannot be extrapolated across species. In the art of gene therapy it has been said over and over that one cannot take data from an experimental animal system and extrapolate to humans (see Orkin et al., first full sentence page 2). In the art of embryonic stem cells, which is closer to the state of the art of the claimed invention, the techniques used to culture ES cells of the mouse were not successful in culturing porcine or ovine ES cells (see Piedrahita et al.).

Applicant cites Gardner, R. L. for a discussion regarding applying techniques of chimera production to numerous species. It is noted that Gardner had great difficulty in **adapting** the technique to rabbits. It should be noted that Gardner first tried to working with rabbit embryos in 1968, but was not successful until 1974. Applicant alleges that Garner's techniques have been used to generate chimeric mice, rats, rabbits, hamsters, sheep, goats, and pigs, however, no references are cited and given the difficulty in applying Gardner's technique to rabbits, it is not clear how much difficulty was encountered in **adapting** the technique to other species. Further, the technique has not been used with primates and given the differences in primate embryology it is unpredictable as to what **adaptations** would be required. Applicant states that human blastomeres behave similarly and have similar nutritional requirements to the blastomeres of other mammalian species. However, this study compares only the culturing of blastomeres up to 138 hours with two different media. It does not take into consideration any manipulation of the embryo other than IVF. It has been acknowledged that one of skill in the art would know the techniques to mix together cells of two species into an aggregate, however, it is not known what would happen next. Even though one may take the culturing techniques used in the field of IVF, it is not known how long an embryo could be cultured and maintain viability. Further, it is not known whether such an embryo would result in a viable pregnancy.

Applicant states that it is certain that inter-genus chimera including human blastomeres will develop to the requisite extent to be useful according to the description (see paper no. 15, page 33). However, such is not certain. In fact the development of inter-species chimera, as claimed, is completely unknown and unpredictable. Applicant states that there is no indication in the literature that a chimera constructed from two mammalian species will not develop to some

extent *in utero*. However, there is nothing in the literature regarding development of a mammalian chimeric embryo where one of the species is human and the other is non-human primate. Applicant says that such chimeras are highly informative objects of study even if they never develop to term. However, it is completely unpredictable that such a chimeric embryo as applicant describes and claims would develop any further than the initial mixing of embryonic cells. Applicant cites the vast increase in knowledge of the early human embryo between 1984 and 1997. However, none of these articles disclose a primate inter-species chimera and none of this art describes primate ES cells as certain claims require.

Applicant argues that all biotechnological procedures are inherently unpredictable. This is not the case. The art of molecular biology is very advanced. Certain aspects of biotechnology are very predictable. Applicant argues that it is inappropriate to require predictability as a condition of patentability. However, predictability and the level thereof is an appropriate factor to consider under 35 USC 112, 1st paragraph as decided by the courts (see *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

Applicant alleges that the level of predictability required by the examiner is not appropriate and is not required for other similar inventions. However, the factors that are being applied to this case are those set forth by the Federal Circuit and are the same as those applied in all other cases.

Applicant maintains that the claimed invention cannot simultaneously be both unpredictable and obvious (see ¶ bridging pages 34-35). However, the breadth of the claims is such that the claims lack enablement and yet would have been obvious to one of ordinary skill in the art. As clearly set forth in the obviousness rejection, the simple mixing of the cells of the two

species falls within the scope of the claims. Because the embryo is by definition considered an embryo from the one cell stage, even the aggregation of cells resulting from the mixing of the two cell species are encompassed by the claims (see the rejection herein under 35 USC 103 and in the previous office action). However, in order for the claims to be enabled the full breadth of the claims must be enabled. This breadth goes much further than simple mixing of cells to include a cooperative being and development into an animal.

Applicant argues that the lack of predictability of the ratio of cells from one or the other species does not impair the usefulness of the invention, since the degree of chimerism can be determined *ex post facto* and will be a relevant variable in many studies performed with these chimeric embryos. However, the embryos must be enabled for use by the description set forth in the specification. If the skilled practician is left to determine how to use the embryo or animal by determining the contribution of the cells in the resultant embryo, then the specification does not enable use of the invention, but instead the skilled practician would have to resort to undue experimentation to first determine how to use the said embryos or animals.

Applicant argues that there is no requirement for implantation of the embryo in order to gain useful information (see paper no. 15, page 36). However, while this may be true in regards to the embryo it is certainly not true in regards to the claims directed to animals. Further, the embryo must be viable long enough to become a cooperative entity in order to gain useful information. As stated previously it is not predictable that the embryo would be viable for this amount of time.

Applicant argues that the degree of predictability necessary to eliminate undue experimentation is a function of the claimed subject matter and its utility. This is true and this is why the invention is rejected under this statute.

Applicant argues that fecundity is not an essential characteristic and that the animals would never breed true because the germ lines would be mosaic. Applicant states that the inability to self-propagate is not a requirement of § 101. However, this rejection is not made under §101. Further, the issue of fecundity is particularly an issue in regards to claim 16 which specifically claims a descendant.

Applicant argues that the feasibility of producing human/non-human animal chimeras is justified by the success of these techniques using mammalian species more distantly related than humans and chimpanzees (see paper no. 15, page 37). However, none of the claims are directed to human/chimpanzee chimeras. The claims, excluding claims 28-34, are directed to human/non-human primate chimeras. Mice and rats, and sheep and goats, are divergent from human/non-human primate chimeras. Sheep and goats are similar in their developmental biology as are mice and rats. Further, these animals are not dissimilar in anatomy and size. However, certain species of primate are vastly different from humans. For instance, spider monkeys, owl monkeys, and squirrel monkeys to name a few. Further, the animals are not similar in developmental timing, anatomy, and size. Even where the species are closely related as human/chimp the outcome is totally unpredictable because the contribution of cells of the two species cannot be predicted. Further, nuances such as the hair covering, the differences in the digits, the sizes of the internal organs may completely preclude formation of an animal and

viability of an embryo. The genetic differences are vast such that it is not clear which genes would regulate maintenance of a viable embryo.

Applicant argues that the contribution of ES cells to the germ line of the resultant animal is not a feature of the invention. However, certain of the claims require the use of ES cells. Further, true primate ES cells are not known. The definition of an ES cell requires contribution to the germ line (see prior office action). Whether this is a feature of the invention or not, the fact that the claims recite ES cells makes this consideration of relevance to the enablement of the claimed invention.

Applicant argues that the criterion of germline transmission has nothing whatever to do with the ability of ES cells to contribute to a chimeric embryo (see paper no. 15, page 38). However, because the claims specifically require the use of ES cells, such cells must be available to the skilled practician. In the instant case they are not because true ES cells are not known in the art for primates.

Applicant points to Wheeler and state that no validation of swine ES cells was made and argue that germline contribution is not a criterion. The examiner does not agree. In all areas where ES cells are discussed it is clearly the goal that these cells are totipotent. Without germline contribution the cells are only characterized as far as pluripotency. Wheeler does teach that chimeric swine were produced and specifically states that the ES cells are pluripotent. It is clear from the Wheeler reference that the ultimate goal is that the ES cells will prove to be totipotent. Until such time it is not clear that the ES cells are true ES cells. Because applicant's claims specifically require the use of these cells, the cells must be true ES cells and must be available. At the time of the invention they were not.

Applicant cites art in which mouse, pig, and two monkeys were disclosed as the source of ES cells. However, the primate cells had not, and still have not, been characterized fully to allow them to be labeled true ES cells.

The examiner is aware of the art in which others were working to develop human ES cells lines. However, in none of these references were the cells characterized as being totipotent. Though it is acknowledged that the cells are pluripotent, ES cells by definition are totipotent. Further, applicant acknowledges that teachings of human ES cells, even though not characterized as totipotent, were not available until after the filing of the instant application. Therefore, the cells were not available for practicing the claimed invention at the time of the invention.

The Bongso reference cited by applicant (see paper no. 15, page 41) is irrelevant because this disclosure relates to ES-like cells. Certain of the claims require ES cells. The Thompson reference to which applicant refers is discussed above. The primate cells have not been shown, even to date, to be totipotent.

The examiner maintains that interspecies chimeras of mouse/rat and sheep/goat cannot be extrapolated to human/non-human primate chimeras. Much of the reasoning is discussed above such as the differences between the developmental embryology of primates in comparison to other mammals, as well as the divergence between the species. Applicant cites Prather et al. as enabling for interspecies chimeras. However, Prather et al. does not disclose any chimeras where human is one of the contributing species and further, Prather et al. discusses only the chimeras discussed above. Though Prather et al. generalizes and makes generic statements regarding mammalian embryo chimeras, these generalities are not considered enabling of a human interspecies chimera.

Applicant argues that mouse/rat or sheep/goat are more distant than human/chimp or human/gorilla. However, no claim is limited as such and if it were it would remain unpredictable for reasons discussed above and previously.

Applicant argues that the art demonstrates that chimeras can be constructed from the blastomeres of more than two individuals from the same species (see paper no. 15, page 44). However, this is not what is claimed. The claims recite more than two species. This is not the same as more than two individuals of the same species. In fact the cited art is limited to mouse. Applicant argues that it is reasonable to expect that any species whose blastomeres can cooperate to form an embryo would give rise to an informative developmental result if cells from three individuals or species were used. However, this is not the case regarding three different species and certainly not the case where one of the species is human and the others are non-human primates because it has not been shown that these interspecific blastomeres would cooperate to form an embryo. Applicant's assumption is flawed because this required data is assumed, but has not been shown.

Applicant argues that in US patent 4,736,866 unpredictable subject matter was granted (see paper no. 15, ¶ bridging pages 45-46). However, each patent application is examined on it's own merits, and in the present case for the reasons set forth above, the specification does not teach one skilled in the art how to make and use the claimed invention.

Applicant alleges that chimeras exist that have been made using primate cells, but do not recite a citation disclosing such (see paper no. 15, page 46). Therefore, the examiner cannot review this data and will not consider the argument. If such data or citation is disclosed in a timely manner the examiner will consider it.

Applicant argues that for pairs such as human/chimp or human/gorilla that share 98 percent DNA homology, the chimera would be expected to develop to birth. However, the DNA homology does not account for anatomical differences, differences in gestation, or more importantly how to get a host mother to carry such a chimera (e.g., immunological differences could cause such a chimera to be aborted by the host mother).

Applicant argues that a chimeric embryo would remain viable long enough to become a cooperative entity (see paper no. 15, page 47). Applicant states that early embryos are extremely resilient to experimental perturbations. However, this is in contrast to other data submitted such as Gardner's data regarding the rabbit embryos. Applicant presents details of a medline search and state that these results demonstrate that non-viability is not a problem. However, such a search is not considered relevant. Negative results are often not reported at all. Where they are reported they may not have been included in the abstract or keyword data such that medline would not have found them. Applicant states that Fassler et al. and Voss et al. were found when they included the phrase "failed to develop" in their search. However, applicant's conclusion that "lack of viability or failure to develop at all is not found when chimeric embryos are constructed" or that "informative partial or full development of the chimeras nonetheless occurs" cannot be based upon these references, nor on the results of the search. Both Fassler et al. and Voss et al. are limited to genetically engineered mice, not interspecies chimeras.

Therefore, the claims stand or are rejected under 35 USC 112, 1st paragraph due to a lack of enabling disclosure for reasons set forth previously and above.

23. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

24. Claims 1-7, 10, 13, 16, 28-34, 38-48, 50, 53, and 55 stand, and newly presented claims 56-71 are rejected under 35 USC 112, 2nd paragraph for reasons of record and as set forth below.

The claims continue to recite the phrase "chimeric embryo". It is maintained that this phraseology renders the claims indefinite because it is not clear when a cell aggregation becomes an embryo. Applicant argues that they consider the term to mean viable, hence an alive embryo (see paper no. 15, page 50). However, this does not address the concern as to when is the cell aggregation actually considered an embryo. The specification does not set forth such a definition. Applicant argues that one of routine skill in the art would be able to use microscopy and histology to make such a determination. However, this is not the case. Even a one-cell fertilized egg cell is considered to be an embryo (see Stedman's Medical Dictionary, 26th edition, at page 559). However, in the instant case the claimed embryos have cells added after this stage. Therefore, it is not clear when the aggregation of cells would be considered a chimeric embryo. The term is interpreted to mean simply a mixture of cells from two individuals.

Applicant's amendment of claim 13 to recite "a chimeric animal derived from a chimeric embryo" is noted. However, the claim remains indefinite. "Derived" is a very vague term that identifies merely a starting source, but could include innumerable changes. It is not clear as to the meets and bounds of the claim.

Applicant's amendment to claim 10 obviates the instant grounds of rejection in regards to the term "generated".

Claims 39-43 are indefinite because the limitation "said embryo is viable no longer than [x] days" is ambiguous. This phrase renders the claims indefinite for at least three reasons. First, the term viable is indefinite as it is used here. Viability is defined as, "Capable of living;

denoting a fetus sufficiently developed to live outside of the uterus." (see Stedman's Medical Dictionary, 26th edition, page 1936). Because the claimed invention is directed to embryos, the term viable would be contradictory to the claimed invention. Secondly, it is not clear how this limitation, being viable no longer than a particular period, affects the nature of the claimed composition. The specification does not address any difference in embryos that are viable for a particular period, thus it is not clear how the composition is affected. The claims do not state that an embryo of any definite age is intended. Third, by stating only that the embryo "is viable" for *x* days, the limitation confusingly suggests that the intent might be to claim a viable embryo no older than *x* days, or, conversely, a non-viable embryo at least older than *x* days.

Claims 44-48 are indefinite because it is not clear how a termination date in intended to affect the claimed embryo. By stating only that the embryo "is terminated on or before day *x*," the limitation confusingly suggests that the intent might be to claim a terminated embryo, or conversely, a non-terminated embryo. The limitation suggests that the intent might be to claim an embryo less than, or conversely, more than a certain age, but the meaning of the claim is unclear.

Claims 60-69 are indefinite because they are composition claims but the statements of uses have no material effect on the composition. If the statements of use are treated as intended uses, they have no material effect on the compositions. It is not clear as to whether applicant intends to claim the products or the methods of use.

Conclusion

25. No claim is allowed.

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Clark whose telephone number is (703) 305-4051. The examiner can normally be reached on Mondays-Fridays from 7:10 a.m. EST to 3:40 p.m. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Deborah Clark

DEBORAH J.R. CLARK
PRIMARY EXAMINER